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Attorney Docket No.: B45182

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Capiau, <i>et al.</i>	March 19, 2002
Serial No.:	09/936,985	Group Art Unit: 1645
Filed:	December 19, 2001	Examiner: V. Ford
For:	Vaccine Against Streptococcus Pneumoniae	

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Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO RESTRICTION REQUIREMENT

Sir:

This paper is in response to the Restriction Requirement dated February 21, 2002. As this response is timely filed within the shortened statutory period for response of thirty (30) days, no fee is required. Please charge any additional requisite fees relating to this amendment and response to Deposit Account No. 19-2570.

Restriction Requirement Under 35 U.S.C. §§ 121 and 372

In response to the Restriction Requirement, Applicants elect Examiner's Group I consisting of Claims 1-9 and 11 with traverse. Moreover, pursuant to the Examiner's requirement under 35 U.S.C. §121 that Applicants elect a single species, Applicants hereby elect Examiner's species F, drawn to CbpA.

Applicants traverse the requirement to restrict and respectfully assert that the "groups of inventions" as described by the Examiner are all linked by a single general inventive concept under PCT Rule 13.1. The Examiner states that the invention set forth in Claim 1 lacks novelty over Paton et al. According to the Examiner's reasoning, since "Group 1 is the main invention in this application and it lacks novelty, . . . the other claims are not so linked by a special technical feature within the

meaning of PCT Rule 13.2 so as to form a single inventive concept". However, Paton et al. only disclose that pneumococcal PS and pneumolysin can be adjuvanted with an approved adjuvant (see WO90/06951, page 4, where Paton et al. teach that the vaccine can be administered "with or without an approved adjuvant, such as alumina gel."). At the priority date of Paton et al., the only approved adjuvant was aluminum hydroxide or phosphate, and it is well known in the art that alumina gel (aluminum hydroxide/alum) is a Th2-type adjuvant (see Vaccine Design: The Subunit and Adjuvant Approach, Powell, M. F. and Newman, M. J. eds. (1995), a copy of which is provided herewith for the Examiner's convenience). There is simply no disclosure in Paton et al. of a Th1-type adjuvant. Therefore, since WO90/06951 teaches only the use a TH2-type adjuvant (the only type approved at the time), Paton et al. does not anticipate the instant claims.

Each of the pending claims teaches the use of a TH1-type adjuvant, and this represents a unanticipated advance over the prior art. Applicants respectfully assert that all of the pending claims are linked by this special technical feature and therefore meet the requirements of unity of invention under the PCT rules. Applicants therefore respectfully request withdrawal of the requirement to restrict (and election of species) and rejoinder of the remaining claims (Claims 12, 14 and 15).

Respectfully submitted,



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Vaccine Design

The Subunit and Adjuvant Approach

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COMPONENT/ADJUVANT NAME: Alhydrogel

OTHER NAME(S): Aluminum hydroxide gel; alum

STRUCTURE: Crystalline aluminum oxyhydroxide $\text{Al}(\text{OOH})_3$, known mineralogically as boehmite. The structure consists of corrugated sheets of aluminum octahedra.



SOURCE: Obtained by precipitation of aluminum hydroxide under alkaline conditions.
USES: Human applications: diphtheria, tetanus, and pertussis vaccines. Veterinary vaccine applications.

APPEARANCE: White gelatinous precipitate in aqueous suspension.

MOLECULAR WEIGHT: Not applicable.

RECOMMENDED STORAGE: 4–25°C. Never expose to freezing. Recommended 2 year shelf life.

CHEMICAL/PHYSICAL PROPERTIES: Primary particles have a rodlike or fibril morphology and a high surface area. The isoelectric point is 11. Its high surface area gives it a high adsorptive capacity for antigen. Poorly soluble in solutions containing citrate ions. Normal particle size range 0.5–10 μm .

INCOMPATIBILITY: Dissolves in strong bases and acids.

SAFETY/TOXICITY: May cause mild local reactions at the site of injection (erythemas and/or mild transient swellings).

- Ganrot, P. O., 1986, Metabolism and possible health effects of aluminum. *Environ. Health Perspect.* 65:363–441.
- Gupta, R. K., et al., 1993, Adjuvants—A balance between toxicity and adjuvanticity. *Vaccine* 11:293–306.

ADJUVANT PROPERTIES: Alhydrogel is the standard preparations for immunological research on aluminum hydroxide gels. The use of aluminum adjuvants is accompanied by stimulation of IL-4 and stimulation of the T-helper-2 subsets in mice, with enhanced IgG1 and IgE production. Further immunomodulation is accomplished by the aluminum content. Properties are described in:

- Shirodkar, S., et al., 1990, Aluminum compounds used as adjuvant in vaccines. *Pharm. Res.* 7:1282–1288.
- Stewart-Tull, D. E. S., 1989, Recommendations for the assessment of adjuvants (immunomodulators), in: *Immunological Adjuvants and Vaccines* (Gregoriadis, G., Allison, A. C., and Poste, G., eds.), Plenum Press, New York, pp. 213–226.
- Gupta, R., et al., Chapter 8, this volume.
- Seeber, S., et al., 1991, Predicting the adsorption of proteins by aluminum-containing adjuvants. *Vaccine* 9:201–203.
- Seeber, S. J., et al., 1991, Solubilization of aluminum-containing adjuvants by constituents of interstitial fluid. *J. Parenteral Sci. Tech.* 45:156–159.
- Hem, S., and White, J. L., Chapter 9, this volume.

CONTACT(S): E. B. Lindblad, Superfos Biosector a/s, DK-2950 Vedbaek, Denmark, Ph: 45 42 89 31 11; Fax: 45 42 89 15 95. Also: AJ Reisch, Sergeant, Inc., Clifton, NJ 07012, Ph: 201-472-9111; Fax: 201-472-5686. Also: Stanley Hem, Purdue University, West Lafayette, IN 47907-1336, Ph: 317-494-1451; Fax: 317-494-7880.

COMPONENT/ADJUVANT NAME: Polysorb

OTHER NAME(S): S

STRUCTURE: An em phosphoric-buffered salt



Polysorb

SOURCE: Oil-in-water emulsions at reduced temperature.

USES: A vaccine adjuvant for cellular and humoral immunity.

APPEARANCE: Homogeneous white emulsion.

MOLECULAR WEIGHT: Not applicable.

RECOMMENDED STORAGE: 4–25°C.

CHEMICAL/PHYSICAL PROPERTIES: Mean diameter around 0.5 μm .

INCOMPATIBILITY: Dissolves in strong bases and acids.

SAFETY/TOXICITY: May cause mild local reactions at the site of injection (erythemas and/or mild transient swellings).

ADJUVANT PROPERTIES: Polysorb is the standard preparation for immunological research on oil-in-water emulsions. The use of oil-in-water emulsions is accompanied by stimulation of IL-4 and stimulation of the T-helper-2 subsets in mice, with enhanced IgG1 and IgE production. Further immunomodulation is accomplished by the oil-in-water emulsion content. Properties are described in:

CONTACT(S): Thermo Scientific, Ph: 92121, Ph: 619-550-1212.